REMARKS

Claims 1-28, 31, 34-50 and 56-68 are pending in the instant application. Claims 42-50 and 56-68 have been withdrawn from consideration by the Examiner and subsequently canceled without prejudice by Applicants in this amendment. Claims 1-28, 31 and 34-41 have been rejected. Claims 8-14 have been canceled. Claims 25 and 27 and the specification have been amended to correct inadvertent typogrpahical errors. No new matter has been added. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Finality of Restriction Requirement

The Examiner has made final the Restriction Requirement mailed March 22, 2002. Accordingly, in an earnest effort to advance the prosecution, Applicants have canceled without prejudice claims 42-50 and 56-68 drawn to nonelected subject matter. However, in light of the finality of this restriction requirement, Applicants reserve the right to file a divisional application to the canceled subject matter.

II. Objection to Drawings

The drawings have been objected to in light of the Draftsperson's Patent Drawing Review. Submission of formal drawings at this point in the prosecution wherein no subject matter has been identified has allowable would be overly burdensome economically to this small-entity, non-profit Applicant.

However, in accordance with the Examiner's request to

provide proposed drawing correction's, Applicants propose to file formal drawings upon receipt of acknowledgment of allowable subject matter with:

acceptable margins, particularly with respect to Figures 3-10 and 13;

lines, numbers and letters which are uniformly thick and well defined, clean, durable and black for Figures 1-14; and

numbers and reference characteristics which are plain and legible for Figures 1-14.

III. Rejection of Claims 1-28, 31 and 34-41 under 35 U.S.C. § 112, first paragraph - Lack of Enablement

Claims 1-28, 31 and 34-41 have been rejected under 35 U.S.C. § 112, first paragraph as the Examiner suggests that the subject matter is "not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner suggests that "the specification does not show any working examples of the claimed method in any protein meeting the claim limitations with respect to a myofilament protein modification product being a chemical adduct of a myofilament protein." The Examiner suggests that "the fact that the claimed method appears to work in troponin is not sufficient to enable the breadth of the claimed method for any and all proteins having a myofilament protein modification product being a chemical adduct of a myofilament protein."

Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully disagree with the

Examiner's suggestion that the disclosure does not clearly identify proteins which qualify as myofilament protein modification products for assessing muscle damage. Further, Applicants respectfully disagree with the Examiner's characterization of the claimed invention and the teachings at page 15, lines 15-18, as a method "directed to any and all proteins having the desired function (association with muscle damage)". Claims of the instant application are not drawn to a method for any and all proteins having a myofilament protein modification product being a chemical adduct of a myofilament protein. Instead, the claims are drawn to a method for assessing muscle damage in a subject by evaluating for the presence or absence of one or more different **myofilament protein modification products** in the biological sample, at least one of said myofilament protein modification products being a chemical adduct of a myofilament protein. Further, what is actually stated at page 15, lines 15-18 of the specification is that:

> The phrase "myofilament protein modification product" is a general term defined as any modification of a myofilament protein associated with muscle damage. Myofilament protein modification products can be chemical adducts of myofilament proteins, degradation products of myofilament proteins, and protein-protein complexes of myofilament proteins.

At page 14, lines 5-10 of the specification the phrase "myofilament protein" is defined as a protein associated with the contractility of skeletal muscle or cardiac muscle cells. A list of exemplary myofilament proteins is also taught therein. Thus, nowhere is it taught or suggested that the method is directed to **any and all** proteins having the desired function.

Instead myofilament protein modification products are clearly identified through the definitions provided at page 14-15.

Applicants also respectfully disagree with the Examiner's suggestion that the disclosure does not identify phosphorylated TnI as a "myofilament modification product being a chemical adduct of a myofilament protein". The specification makes clear throughout that phosphorylation of a myofilament protein is considered a myofilament protein modification product and a chemical adduct of a myofilament protein. See for example page 11, lines 11-12 and 23-24 of the specification, wherein it is taught that "[m]ore preferably, the chemical adduct is a phosphorylated form of troponin I, troponin T or tropomyosin." Also see page 14, lines 11-25 wherein a list of exemplary chemical adducts inclusive of the post-translational modification of phosphorylation is provided.

Further, with respect to Example V, the fact that intact troponin I is also detectable in human myocardium following MI is irrelevant to enablement of the claimed method. As acknowledged by the Examiner in the Office Action, Example V teaches that dephosphorylated TnI, as well as protein-protein complexes involving TnI were measured. Further, it is taught in Example V, that dephosphorylated TnI resulted from dephosphorylation of the phosphorylated TnI modification product by alkaline phosphatase. Thus, this Example is clearly demonstrative of the ability to assess for the presence or absence of one or more different myofilament protein modification products, at least one of which is a chemical adduct of a myofilament protein, in damaged muscle tissue. In addition to Example V, Example II at pages 36-38 of

the specification also teaches detection of TnI and its phosphorylated modification products in damaged muscle tissue.

In addition, contrary to the Examiner's suggestion that the specification exemplifies troponin only, Applicants respectfully direct the Examiner to Example I at pages 31-35 of the specification wherein detection of a MLC1 modification product in damaged muscle tissue is taught and Example IV at pages 48-49 of the instant specification wherein detection of a post-translationally modified form of troponin T is taught.

Thus, all reasoning provided by the Examiner to question the enablement of the instant invention is based upon a mischaracterization of the claimed invention and the definitions provided in the instant specification as well as a misinterpretation of the significance of some reported data and failure to consider all data taught in the specification. Accordingly, since the Examiner has provided no reasonable basis to question the enablement of the claimed invention, as required by MPEP §2164.04, withdrawal of this rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

The Examiner also suggests that the specification is not enabling for the Mab monoclonal antibodies 8I-1 and 2I-14 because the instant specification is not in compliance with the biological deposit rules.

Applicants respectfully traverse this rejection.

Antibodies 8I-1 and 2I-14 are known and readily available to the public through commercial sources such as Spectral Diagnostics Inc. Evidence of their commercial availability is provided in the specification at page 34, lines 1 and 22 and pages printed recently from their Web-site, a copy of which is

provided herewith. Further, these antibodies are priced to allow access by the public. Thus, in accordance with MPEP 2404.01, deposit of these antibodies is not required.

Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is therefore respectfully requested.

IV. Rejection of Claims 1-28, 31 and 34-41 under 35 U.S.C. § 112, first paragraph - Written Description

Claims 1-28, 31 and 34-41 have been rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner suggests that "the claims and specification fail to provide the identity or structure of these myofilament modification product being a chemical adduct of a myofilament protein."

Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Examiner's suggestion that the specification must state the identity by sequence or any structural characteristics of any other protein meeting the claimed characteristic of a myofilament protein modification product being a chemical adduct of a myofilament protein. At page 15, lines 15-18, the phrase "myofilament protein modification product" is defined as any modification of a myofilament protein associated with muscle damage. Myofilament protein modification products can be chemical adducts of myofilament proteins, degradation products of myofilament

proteins, and protein-protein complexes of myofilament proteins. Further, at page 14, lines 5-10, the phrase myofilament protein is defined as any protein associated with the contractility of a skeletal or cardiac muscle cell and is inclusive of an extensive list of myofilament proteins, the structural characteristics and sequences for which are well known to those skilled in the art. Accordingly, inclusion of their sequences and structural characteristics is not required. Finally, at page 14, lines 11-26, the phrase "chemical adducts of a myofilament protein" is defined and is inclusive of an extensive list of post-translational modifications, the structures for which are again well known to those skilled in the art.

Further, the Example section of the application provides detailed methodologies for experiments wherein a myofilament protein modification product being a chemical adduct of a myofilament protein was detected in damaged muscles. Example II and V teach detection of TnI and its phosphorylated modification products in damaged muscle tissue. Example I teaches detection of a MLC1 modification product in damaged muscle tissue. Example IV teaches detection of a post-translationally modified form of troponin T.

Thus, the instant specification clearly establishes that Applicants were in possession of the claimed invention. Withdrawal of this rejection under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

The Examiner suggests that "the written description in this case only sets forth Mab monoclonal antibodies 8I-7 and 2I-14 and therefore the written description is not commensurate in scope with the claims drawn to any compound that specifically binds the

myofilament protein modification product." In an earnest effort to advance the prosecution of this case, Applicants have canceled those claims drawn to any compound that specifically binds the myofilament protein modification product. Withdrawal of this rejection is also therefore respectfully requested.

V. Rejection of Claims under 35 U.S.C. § 102(a)

Claims 1, 8-10, 15-16, 19-21, and 34-37 have been rejected under 35 U.S.C. § 102(a) as being anticipated by McDonough et al. (Circulation Research, January 8/22, 1999, pages 9-20). The Examiner suggests that "McDonough et al. disclose troponin I modifications which were responsible for the contractile dysfunction in myocardial ischemia/reperfusion injury."

Applicants respectfully traverse this rejection.

The reference of McDonough et al. is Applicant's own work. Applicants are submitting a Declaration in accordance with *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982) establishing that Jason L. McDonough and D. Kent Arrell were named as co-authors of this paper for their involvement in assays and tests described in this paper, but not as inventors since they did not participate in the conception of this invention. This Declaration further establishes that co-author Jennifer Van Eyk, as well as Ralf Labugger and Irina Neverova are properly named as co-inventors of the instant patent application for their participation in the conception of the claimed invention. Thus, the reference of McDonough et al. is not a valid prior art reference under 35 U.S.C. § 102(a).

Withdrawal of this rejection is therefore respectfully

requested.

VI. Rejection of Claims under 35 U.S.C. § 103(a)

Claims 2-5, 7 and 38-40 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over McDonough et al. in view of Wicks et al. (U.S. Patent 5,834,220). The Examiner suggests that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure two different myofilament product degradation products (troponin I and troponin C) in muscle damage as taught by Wicks et al. in the method of McDonough et al., involving troponin I analysis because Wicks et al. taught that troponin I is one of three subunits of the troponin complex." The Examiner suggests that "one having ordinary skill in the art would have been motivated to do this to acquire the enhanced sensitivity and ability to reduce false positives while providing more data sets for analysis, wherein accurate and precise detection is available."

Claims 6, 11-14, 17-18, 22-28, 31 and 41 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over McDonough et al. in view of Wicks et al. and further in view of Van Eyk et al. (U.S. Patent 6,248,549). The Examiner suggests that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure two different myofilament product degradation products from different protein with respect to their phosphorylation states (troponin I and calponin) in muscle damage as taught by Van Eyk et al. in the method of McDonough et al. in view of Wicks et al. to detect troponin I analysis because Van Eyk et al. taught that such

method configurations allowed for the assessment of compositions in a screening format for their effect on PAK kinase activity or expression with respect to muscle disorders."

Applicants respectfully traverse these rejections.

As discussed in Section V, *supra*, McDonough et al. is the inventors' own work and therefore is not a valid prior art reference with respect to the instant application. Accordingly, this reference cannot be cited in combination with Wicks et al. or Wicks et al. and Van Eyk et al.

Further, neither Wicks et al. nor Van Eyk et al. teach or suggest detecting a myofilament protein modification product which is a chemical adduct of a myofilament protein to diagnose muscle damage.

Accordingly, these secondary references alone fail to provide the requisite teaching or suggestion of all claim limitations to render obvious a claim drawn to a method for assessing muscle damage by evaluating for the presence or absence of one or more different myofilament protein modification products in the biological sample, wherein at least one of the myofilament protein modification products is a chemical adduct of a myofilament protein. See MPEP § 2143.

Withdrawal of these rejections under 35 U.S.C. § 103(a) is therefore respectfully requested.

VII. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record.
Accordingly, favorable reconsideration and subsequent allowance

of the pending claims is earnestly solicited.

Respectfully submitted,

Kathleen A. Tyrrell
Registration No. 38,350

Date: June 9, 2003

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Our primary research has been focused on the development of immunoassays for cardiac and other disease related markers. The process can be divided into three stages: generation of antigens and antibodies, assay development and clinical studies. Spectral realizes that the generation of superior reagents is the key to developing high quality clinical diagnostic products.

Throughout the diagnostic industry, antigens are generally purified from animal or human tissues. This process is laborious and often results in low protein yields. Spectral has built a strong molecular biology and protein chemistry team. With the latest recombinant technology Spectral not only has engineered and produced over 30 antigens in bacteria successfully but also has created several patented novel molecules, which show superior performance over their native counterparts. As an example, Spectral's single-chain troponin I-C polypeptide has been recognized by the market as the best calibrator and control material for cardiac troponin I immunoassays. The same material has been selected by the American Association of Clinical Chemistry as one of the three candidate international standard materials for troponin I immunoassays.

Spectral also has an excellent in house antibody generation and assay development team. Over 90% of the antibodies used in our commercial kits are generated in house. Spectral uses two platforms to evaluate antibodies and recombinant proteins. The first is a Biacore Biosensor, which aids in the identification and pairing selection of high affinity monoclonal antibodies. This biosensor also assists in the comparative analysis of recombinant proteins and their native counterparts. Our latex homogenous assay system rounds out our platforms for reagent analysis. This system allows us to quickly evaluate reagents in a clinical analyzer format.

Spectral's R&D team is organized in specialized groups and the interaction among groups is project oriented. Spectral scientists are continuously trained by periodic scientific seminars and by attending scientific workshops and conferences. Spectral's projects are managed following ISO 9001 standards and the performance of Spectral's quality system is monitored by regular internal and external quality audits.

Monoclonal Antibodies **Polyclonal Antibodies** **Recombinant Proteins**

Spectral Diagnostics has additional antibody clones available. Please contact us to receive a complete list of available antibodies or for a custom set of monoclonal antibodies for your specific needs.

Monoclonal Antibodies

Specificity	Clone No.	Catalogue No.
Cardiac Troponin I	21-14	MA-1010
Cardiac Troponin I	31-265	MA-1020
Cardiac Troponin I	31-59	MA-1030
Cardiac Troponin I	81-7	MA-1040
Cardiac Troponin I	3E3	MA-1050
Skeletal Troponin I	F1-23	MA-1110
Skeletal Troponin I	F1-32	MA-1120
Myogl bin	2MB-295	MA-2010

Myoglobin	4MB-154	MA-2020
Myoglobin	5MB-64	MA-2030
Myoglobin	9MB-183	MA-2040
My gl bin	18MB-35	MA-2050
CK-MB	2CKMB-240	MA-3010
CK-MB	6CKMB-19	MA-3020
CK-MB	6CKMB-53	MA-3030
CK-MB	13CKMB-170	MA-3040
CK-MM	5CKMM-215	MA-3110
Carbonic Anhydrase III	2CA-4	MA-4010
Carbonic Anhydrase III	2CA-2	MA-4020
Carbonic Anhydrase III	2CA-10	MA-4030
Myosin Light Chain I	39-15	MA-5010
Myosin Light Chain I	5LC-3	MA-5020
Myosin Light Chain I	1LC-14	MA-5030
Fatty Acid Binding Protein	9FABP-60	MA-6010
Fatty Acid Binding Protein	1rFABP-299	MA-6020
Fatty Acid Binding Protein	9FABP-125	MA-6030
Glycogen Phosphorylase BB	BB-1F9	MA-7010
Cytochrome C	2CYTC-199	MA-8010
Cytochrome C	4CYTC-21	MA-8020

Polyclonal Antibodies

Specificity	Catalogue No.
Troponin I	PA-1010
Troponin I	PA-1020
Myoglobin	PA-2010
CK-MM	PA-3110
Carbonic Anhydrase III	PA-4010
Fatty Acid Binding Protein	PA-6010
Glycogen Phosphorylase BB	PA-7010

Recombinant Proteins

Pr duct Description	Catalogue Number
Carbonic Anhydrase III	RP-1000
Creatine Kinase BB	RP-2000
Single Chain Creatine Kinase MB	RP-2100
Creatine Kinase MB	RP-2400
Single Chain Creatine Kinase MB	RP-2500
Creatine Kinase MM	RP-2600
Cardiac Troponin CIT Complex	RP-3000
Cardiac Troponin C	RP-3200
Cardiac Troponin C-I Complex	RP-3300
Cardiac Tr p nin I	RP-3400
Cardiac Single Chain Tn I-C-1	RP-3500

Cardiac Troponin T	RP-3600
Cardiac Single Chain Tn I-C-2	RP-3700
Fast Skeletal Trop nin I	RP-3800
Muscle Fatty Acid Binding Pr tein	RP-4000
Glycogen Phosphorylase BB (assay grade)	RP-5000
Glyc gen Ph sph rylase BB	RP-5100
Ventricular Myosin Light Chain 1	RP-6000
My gl bin (without heme)	RP-7000
Myoglobin	RP-7500
ProBNP	RP-8000
NT-proBNP	RP-8100
Streptavidin-NC	RP-9000
Note:	All recombinant proteins are produced in E.coli and cloned from human cDNA library except Streptavidin

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#24

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Considered LVCook 8/22/03

Attorney Docket No.:	PTQ-0028
Inventors:	Van Eyk et al.
Serial No.:	09/419,901
Filing Date:	October 18, 1999
Examiner:	Cook, Lisa V.
Group Art Unit:	1641
Title:	Methods of Diagnosing Muscle Damage

Dear Sir:

DECLARATION BY JENNIFER E. VAN EYK

I, Jennifer E. Van Eyk hereby declare:

1. I am a co-inventor on the above-referenced patent application with Ralf Labugger and Irina Neverova and am familiar with the conception and reduction to practice of the claimed invention.

2. I am also a co-author with Jason L. McDonough and D. Kent Arrell of the 1999 publication in Circulation Research, Vol. 84, pages 9-20.

3. Jason L. McDonough and D. Kent Arrell are named as co-authors of this paper for their contribution to assays and tests described in this paper.

4. However, as they did not participate in the conception with Ralf Labugger, Irina Neverova and me of the claimed invention of the above-referenced patent application, they are not inventors of this patent application.

I hereby declare that all statements herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful statements and the like so made are punishable by fine or by imprisonment, or both, under §1001 of Title 18 of the United States code, and that such willful statements may jeopardize the validity of the

application, any patent issuing there upon, or any patent to which this verified statement is directed.

J. Van Eyk

Jennifer E. Van Eyk

June 9, 2003

Date